PC9563AJTJ

#30
2-6-02
1 of 3

IN THE UNITED STAES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE APPLICATION OF: :
YESOOK KIM Examiner: E. White

SERIAL NO.:**08/850,353** :

FILED: **MAY 2, 1997** : Art Unit: 1623

FOR: **METHOD OF SELECTING A SALT FOR MAKING AN INCLUSION COMPLEX**

Assistant Commissioner for Patents
Washington, D.C. 20231

BRIEF FOR APPELLANTS
UNDER 37 C. F. R. §1.192 (a)

James T. Jones
Registration No. 30,561
Pfizer Inc.
Patent Department
Eastern Point Road
Groton, CT 06340
(860) 441-4903
PATENT

TABLE OF CONTENTS

IN THE UNITED STAES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE APPLICATION OF: :
Yesook Kim . Examiner: E. White

SERIAL NO.:**08/850,353** :

FILED: **May 2, 1997** : Art Unit: 1623

FOR: **Method of Selecting a Salt for Making an Inclusion Complex**

Assistant Commissioner for Patents
Washington, D.C. 20231

APPELLANTS' BRIEF
UNDER 37 C.F.R. §1.192 (A)

A. REAL PARTY IN INTEREST

The real party in interest of the above-referenced application is Pfizer Inc. by virtue of an assignment executed by the inventor, Yesook Kim, recorded at Reel/Frame 7971/0758.

B. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences presently pending which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant pending appeal.

C. STATUS OF CLAIMS

Claims 1, 2, and 3 are currently on appeal.

Of these, claims 1 and 2 stand rejected under 35 USC §112, second paragraph.

All of claims 1 through 3 stand rejected under 35 USC §103(a) over a single reference, US 5,624,940 to Bryant.

Claims 4 through 15 were canceled without waiver or prejudice in Appellant's amendment Dated May 4, 1999. Hence these claims are not on appeal.

D. STATUS OF AMENDMENTS

No amendment was entered, or entry attempted, after a Final rejection.

For completeness, it is noted that all amendments proposed during prosecution prior to Final rejection were entered. A copy of claims 1-3, i.e., all claims on appeal, is included with this Brief as Appendix A.

E. SUMMARY OF THE INVENTION

The invention relates to a method of selecting a salt, from among a series of salts, which has a solubility in a cyclodextrin equal to or greater than a desired target solubility. The invention is based, *inter alia*, on the finding that there are differences in equilibrium solubility among the salts of a given drug in a specific cyclodextrin. That is, Appellant made the determination that different salts of a given compound can have different solubilities in the same cyclodextrin. The art previously believed that a salt of a drug dissolves in a cyclodextrin-containing aqueous media by simply dissociating to form a charged drug molecule and a counter-ion, and that the dissociated (i.e., charged) drug molecule is the guest moiety which forms the inclusion complex with the cyclodextrin. A consequence of this belief was the corollary belief that there are no differences in equilibrium solubility among the various salts of a given drug in a specific cyclodextrin. This is explained in Appellant's specification on page 2, lines 14-27, as follows:

> Many medicinal compounds, when salt formation is feasible, are administered in the form of one or another of their pharmaceutically acceptable salts. Not all such salts are freely soluble in aqueous media, however, and accordingly complexation of the salt of interest with a cyclodextrin is often explored as a means to increase the salt's aqueous solubility. It is conventionally believed that a salt of a drug dissolves in a cyclodextrin-containing aqueous media by simply dissociating to form a charged drug molecule and a counter-ion, and that the dissociated (i.e., charged) drug molecule is the guest moiety which forms the inclusion complex with the cyclodextrin. A consequence of this is the belief that there are no differences in equilibrium solubility among the salts of a given drug in a specific cyclodextrin. Thus, if a solubility-phase diagram is generated for a particular drug in a particular aqueous cyclodextrin (i.e., a plot of the maximum equilibrium solubility of a drug salt in the aqueous cyclodextrin as a function of cyclodextrin concentration),

different salts of the drug should plot out as lines having the same slope.

As a consequence of the foregoing beliefs, the art nowhere discloses locating a salt having a solubility greater than a threshold solubility (i.e. greater than a desired target solubility), by Appellant's method or anything approaching it.

F. THE ISSUES

1. Whether claims 1-2 are indefinite under 35 USC §112 in their use of the phrase "desired target solubility".
2. Whether claims 1-3 are obvious over Bryant, US 5,624,940.

G. GROUPING OF THE CLAIMS

Claims 1 and 2 constitute a first group.

Claim 3 constitutes a second group.

The rationale behind the above grouping is as follows. Only claims 1 and 2 stand rejected under 35 USC §112. Claim 3 was not rejected under §112. By contrast, all three claims stand rejected under 35 USC §103. If (1) all three claims are grouped together, (2) the Board reverses the rejection under §103, but (3) affirms the rejection under §112, then claim 3 would fall with claims 1 and 2 under the foregoing scenario even though the only (i.e., the §103) rejection against claim 3 was reversed. In the event the foregoing scenario does in fact occur, Appellant desires at least to gain the allowance of claim 3, and is accordingly requesting to group it separately from claims 1 and 2.

H. ARGUMENT

(1) CLAIMS 1 AND 2 ARE NOT INDEFINITE UNDER §112, SECOND PARAGRAPH.

THE REJECTION

Before Appellant sets forth her argument, and for the sake of convenience, it would be useful to review the rejection. The substance of the

rejection can be summarized by the following quotation taken from the Office Action of June 17, 1999:

> Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
>
> The metes and bounds of the term "desired target solubility" in claims 1 and 2 cannot be determined which renders the claims indefinite. The terms "desired target solubility" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. [6/17/99 Office Action, page 2]

The Examiner continued to maintain the rejection throughout prosecution, stating in pertinent part, for example, in the Office Action of February 7, 2000, that:

> "Applicant argues against this rejection on the grounds that the term "desired target solubility" was completely clear and distinct without the abundant explanation given in Applicant's specification, but that, especially in light of the explanation (and exemplification) of "desired solubility" supplied by Applicant in the specification, one skilled in the art, would find the claims to be clear and distinct, and have no difficulty understanding the metes and bounds of the subject matter claimed. However, this argument is not persuasive since the metes and bounds of the term "desired target solubility" cannot be determined without further explanation in the claims as to the exact solubility that is desired by the Applicant. Furthermore, this terminology does not fulfill the requirement of 35 U.S.C. 112, second paragraph, since this language does not point out and distinctly claim the subject matter and the specification does not provide a standard for ascertaining the requisite degree of the term. [Page 2, paragraph 6 of the 02/07/00 Official Action].

ARGUMENT

The rejection should be reversed on the basis that one skilled in the art, particularly in view of the explanation and definition given in the specification, would readily understand the meaning of the term "desired target solubility", and thus be able to determine the metes and bounds of the claims. It is noted that this is all that the second paragraph of § 112 requires

- - that the claims set out and circumscribe a particular area that the Appellant regards as the invention with a reasonable degree of precision and particularity. See In re Borkowski, 164 USPQ 2d 642 where it was stated

> The first sentence of the second paragraph of §112 is essentially a requirement for *precision* and *definiteness* of claim language. If the scope of subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends that claim to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which the applicant regards as his invention. [164 USPQ at 645-46; emphasis in original]

The Examiner, as quoted above, has taken the position that the term "desired target solubility" does not point out and distinctly claim the invention because (1) the term cannot be determined without further explanation in the claims as to the exact solubility that is desired by the Appellant. and (2) the specification does not provide a standard for ascertaining the requisite degree of the term.

Appellant takes the position that (1) an Applicant is allowed to be his own lexicographer; (2) definiteness of claim language must be analyzed not in a vacuum, but in light of the specification and the prior art; (3) it is the function of the specification to explain the meaning of terms, not the claims; and (4) Appellant has gone out of her way in her specification to explain and exemplify exactly what is intended by the phrase at issue.

With regard to Appellant's point (1), it is well accepted that an applicant can define her own terms, i.e. she can be her own lexicographer. See Beachcombers, International, Inc. v. WildeWood Creative products, Inc., 31 USPQ2d 1653, at 1656 (Fed Cir 1994) where the court stated:

> As we have repeatedly said, a patentee can be his own lexicographer provided the patentee's definition, to the extent it differs from the conventional definition, is clearly set forth in the specification_

Thus, as a threshold consideration Appellant was clearly permitted to use the phrase "desired target solubility", particularly since she went out of her way to define the term, as more fully explained below.

With regard to point (2), Appellant's claim language is interpreted in light of the specification. Georgia Pacific Corp. v. United States Plywood Corp., 118 USPQ 122 (2d Cir. 1958)

> [o]n the other hand, patentable inventions cannot always be described in terms of exact measurements, symbols, and formulae, and the applicant necessarily must use the meager tools provided by language, tools which admittedly lack exactitude and precision. If the claims, **read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more.** [emphasis supplied]

Appellant has in fact gone out of her way to ensure that the term "desired target solubility" would be well understood. This point is amplified and explained further below.

With regard to Appellant's point (3), further explanation is not required to be placed in the claims, as implicitly contended by the Examiner (see, for example, the Office Action dated February 7, 2000. Enablement and description, including explanation, are the functions of the specification. As stated above, Appellant has gone to great lengths to ensure that the phrase "desired target solubility" would be well understood by an interested reader. The claim is otherwise clear and distinct and those skilled in the art would have no difficulty understanding the subject matter intended. That is all that the second paragraph of §112 requires. The Patent Act "requires only reasonable precision in delineating the bounds of the claimed invention." United States v. Teletronics, Inc., 8 USPQ2d 1217 (fed. Cir. 1988). Also,

> The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification... If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, §112 demands no more.

See Miles Laboratories Inc. v. Shannon Inc., 27 USPQ2d 1123 (Fed. Cir. 1993), at page 1126.

With regard to Appellant's point (4), See page 4, line 25 to page 5, line 14 of the application where it is stated:

> A "desired target solubility" as used herein can be a mimimum solubility, usually pre-determined or pre-chosen, required for the compound being tested. The required minimum solubility will generally be chosen on the basis of therapeutic need. For example, assume that it is desired to administer 20 mg of a compound ("Compound X") parenterally, by injection, and that it is desired to administer an injection volume of not more than 2 ml to minimize pain on injection. Thus a salt of Compound X, in order to be "useful", would need to have a solubility, in the chosen aqueous cyclodextrin, equivalent to or greater than 10 mg/ml of Compound X in its active form.
>
> Within a given series of salts, the most soluble salt may not be the most useful candidate for a given application. Factors such as chemical stability, hygroscopicity, and the potential for precipitation may also be considered and weigh in favor of choosing a candidate having a solubility greater than the target solubility, but less than the maximum determined within the series.
>
> On the other hand, at times it may indeed be desired simply to find the salt with the highest solubility of all salts within a series of salts of a particular compound. In this case the "desired target solubility" is simply the highest solubility encountered in the series of salts by comparison of equilibrium solubilities among the various salt candidates. For example, if it is desired to make a dry oral dosage form such as a capsule or tablet using an inclusion complex of a salt of Compound X, then it may be desired simply to find the most soluble salt available in order to minimize the amount of inclusion complex in the dosage form, and thereby minimize the size of the dosage form itself.

The above quotation represents an extensive, illustrated, explanation which would render the meaning of "desired target solubility" clear to anyone skilled in the art, and which is sufficient to explain to anyone skilled in the art just exactly what is intended. Appellant has defined the term extensively and even explained how and why one would go about determining a desired target solubility. The above quotation illustrates that Appellant has gone to great lengths to make sure that the phrase "desired target solubility" is fully understood within the context of the instant invention. The first paragraph notes that a desired target solubility will generally be some pre-determined or pre-chosen solubility selected on the basis of therapeutic need, and gives a hypothetical numerical example to illustrate exactly what is intended. The next paragraph explains that the salt having the maximum solubility determined within a series of salts may not always be selected simply

because it is the maximum. Other factors, for example chemical stability, hygroscopicity, and the potential for precipitation, are mentioned which may weigh in favor of choosing a candidate having a solubility greater than the target solubility, but less than the maximum solubility determined within a series of salts. The skilled art worker reading Appellant's disclosure would immediately realize that a "desired target solubility" is a threshold solubility needed to effect therapeutic efficacy in a dosage form, the threshold being the desired target solubility. The skilled worker would also realize that the actual salt selected need not be the most soluble salt found so long as its solubility meets or exceeds the target solubility.

Appellant further included a detailed example, Example 3, which goes into great detail as to how salts having a desired target solubility would be chosen for adult and pediatric patient subsets when, because of differing therapeutic requirements for each different patient subset, the desired target solubility differs as well with respect to each subset. The example discloses a series of salts (i.e., Salts A through E) and explains exactly how desired target solubilities, and salts satisfying such targets, would be chosen. The example thus adds understanding to the already well-explained term at issue.

For all of the above reasons, it is respectfully submitted that the rejection under §112 is simply not tenable for this application, which was originally drafted to ensure that the disputed term "desired target solubility" would in fact be well understood. In view of the above comments, it is requested that the rejection under 35 USC §112 be reversed.

(2) CLAIMS 1, 2, AND 3 ARE UNOBVIOUS OVER US 5,624,940 (BRYANT et al)

DISCUSSION OF THE APPLIED ART OF RECORD

Prior to offering Appellants' arguments, it would be useful to review the applied art of record, i.e., Bryant et al (hereinafter "Bryant). Bryant discloses a series of benzothiophenes or a salt thereof which have low water solubilities. Bryant further discloses a list of acid salt counterions starting at column 3, line 8. Specific salts are not disclosed in this section. The claims

and disclosure feature an aqueous inclusion complex containing the benzothiophene *per se* or a salt thereof. Bryant thus appears to be neutral as to whether his inclusion complexes are made with his compound of formula (I) or with a salt thereof, and therefore contains no particular teaching that a salt should be used as opposed to the impliedly neutral compound. Indeed, the only specific salt Bryant actually discloses is the hydrochloride salt of a particular benzothiophene known as Raloxifene (column 3, lines 58-62; Example 1; the claims). Further, Bryant (1) never suggests that any particular salt of a compound of formula (I) is any more soluble in cyclodextrin than any other salt made with any other counterion also disclosed therein, (2) never touches on how such a salt would be located, and (3) never even remotely suggests the possibility or feasibility of doing so. Bryant neither discloses, suggests, nor motivates anything relating to Appellant's method, and without such disclosure, suggestion or motivation, Appellant's position is that it is simply not possible for Bryant to render compositions comprising such salts and cyclodextrins obvious.

ARGUMENT

First, it is again emphasized that the invention is based, *inter alia*, on the recognition by Appellant that different salts of a given compound can have different solubilities in the same cyclodextrin. Without the recognition that such solubilities can differ, a method for determining a solubility in excess of a desired target solubility cannot be obvious. Bryant certainly contains no such recognition.

In discussing Appellant's Argument, it would be useful and convenient to reproduce claim 1:

> 1. A method of locating one or more salts of a compound, said salts having a solubility in a cyclodextrin equal to or greater than a desired target solubility, comprising obtaining a series of salts of said compound, determining the equilibrium solubility of each salt in said series in an aqueous solution of said cyclodextrin, and comparing each measured solubility with said target solubility.

Bryant does not disclose "obtaining a series of salts of said compound", as required by Claim 1. Nor does Bryant disclose "determining

the equilibrium solubility of each salt in said series in an aqueous solution of said cyclodextrin", as also required by Claim 1. Nor does Bryant disclose "comparing each measured solubility with said target solubility" as also required by Claim 1. None of these elements is disclosed or suggested by Bryant, and the Examiner has provided no basis for arguing or concluding otherwise. The same or similar arguments can be made for claims 2 and 3. Because Bryant does not disclose or suggest these claim elements, it is simply not seen how Appellant's invention can be obvious, and the rejection should be reversed on that basis.

The rejection should further be reversed on the basis that Bryant does not disclose that different salts of the same compound have different solubilities in the same cyclodextrin, and, for that matter, teaches nothing relating to determining any solubility above any minimum or threshold level, i.e., Bryant discloses nothing relating to determining a desired target solubility.

An additional comment is in order relating to the following Examiner's comments in paragraph 8 of the February 7, 2000 Office Action:

> The claims do not specific [sic: specify] any particular salt of a compound and only indicates that the salts of the compound are being made soluble by combining the salts of the compound with cyclodextrin, which is well known in the art as indicated in the Bryant et al patent. The fact that Applicants are determining the solubility of a series of salts (which have not been specifically set forth in the claims) does not make the claims patentable over the prior art. [page 3 (paragraph 8) of the 02/07/00 Office Action]

The Examiner appears to be requiring that Appellant amend her claims to specify particular salts. Such (1) should not be required because the prior art (Bryant) does not warrant it, and (2) such an amendment would, in effect, unjustifiably deprive Appellant of the broad scope to which she is entitled. Appellant's method is intended to be general so that it can be used to find a useful salt (i.e., one having a solubility equal to or greater than a desired target solubility) for any compound. The method is not limited to any particular salts or to any particular compounds. Because of the method's generality, it would totally defeat the purpose of the invention to specify particular salts in the claims, and thereby limit the claims, as suggested by the

Examiner. It would be equally self-defeating to specify a particular "series of salts" in the claims, as also implicitly suggested by the Examiner. That would again needlessly limit the claims to that particular series of salts even though the invention does not reside in any particular series of salts. The point is that it would not be obvious to test a series of salts to see which one exceeds a pre-determined or desired (i.e., target) solubility if conventional wisdom was that the salts would all have the same solubility in the first place.

Bryant does nothing to bridge the gap between the prior art and Appellant's invention. Bryant simply teaches a genus of compounds, notes that the compounds can form the usual pharmaceutically acceptable acid addition and base addition salts, and discloses that cyclodextrin inclusion complexes can be made. Bryant discloses nothing about any one salt of a compound having a greater solubility in a given cyclodextrin than any other. Bryant discloses nothing about any method for making such a solubility determination within a series of salts, and fails to even remotely mention the feasibility for doing so. There is emphatically no disclosure, teaching or recognition in Bryant that any salt of a given compound would be any more or less soluble in a given cyclodextrin than any other salt in the same cyclodextrin. There is not even the slightest indication that different salts of the same compound can have different solubilities in a given cyclodextrin, i.e., of the very finding that, *inter alia*, underlies Appellant's invention.

It is noted that in the Advisory Office Action dated May 30, 2000, the Examiner made the following (handwritten) statement:

> Bryant is drawn to the selection of useful salt inclusion complexes of cyclodextrin, and therefore meets the claims. While Bryant et al does not de-select any salts, neither does the process of the present invention.

With respect to Appellant's claims 2 and 3, the above statement is simply wrong in the conclusion that "...neither does the process of the present invention". Both claims specifically require a "selecting" step, see step (c) in claim 2 and step (f) in claim 3. The process of selecting, in turn, implies that a "de-selection" of other salts may need to be made, i.e., if such other salts do not have a solubility equal to or greater than a desired target solubility.

Claim 1 does not employ the word "select", as do claims 2 and 3. That is immaterial, however, since Bryant fails to disclose any of the other steps required by claim 1 - - obtaining a series of salts, determining the equilibrium solubility of each salt in the series in an aqueous solution of a given cyclodextrin, and comparing the equilibrium solubility of the measured solubility with a target solubility.

The Examiner is also in error in stating that "Bryant is drawn to the selection of useful salt inclusion complexes of cyclodextrin..." Bryant simply discloses that cyclodextrin complexes of different salts of his formula (I) compounds can be made. Bryant never discloses selecting anything, including "selecting" any cyclodextrin complex relative to any other. Simply disclosing salts and disclosing cyclodextrins which can be used to complex the salts is not the same as "selecting", and the Examiner has not provided any basis otherwise.

In summary, Bryant, read in context, (1) never suggests that any particular salt of a compound of his formula (I) is any more soluble in a given cyclodextrin than any other salt made with any other acid or base also disclosed therein, (2) never touches on how such a salt would be located, and (3) never even remotely suggests the possibility or feasibility of doing so. Bryant neither discloses, suggests, nor motivates anything relating to Appellant's method, and could not without a recognition of Appellant's finding, discussed above, that different salts of a given compound have different solubilities in the same cyclodextrin. Again, the Examiner has provided no basis otherwise. Without such suggestion or motivation it is simply not possible for Bryant to render Appellant's method obvious.

Accordingly, it is respectfully requested that the rejection of claims 1-3 be reversed.

CONCLUSION

For the reasons discussed above, it is respectfully requested that the indefiniteness rejection of claims 1 and 2 under §112 be **reversed.**

For the reasons discussed above, it is respectfully requested that the rejection of claims 1, 2, and 3 as obvious over US 5,624,940 be **reversed.**

Respectfully submitted,

Date: February 5, 2002

James T. Jones
Attorney for Appellants
Reg. No. 30,561

Pfizer Inc
Patent Department
Eastern Point Road
Groton, CT 06340
(860) 441-4903

APPENDIX A - Claims on Appeal

What is claimed is:

1. A method of locating one or more salts of a compound, said salts having a solubility in a cyclodextrin equal to or greater than a desired target solubility, comprising obtaining a series of salts of said compound, determining the equilibrium solubility of each salt in said series in an aqueous solution of said cyclodextrin, and comparing each measured solubility with said target solubility.

2. A method of determining a useful salt, from within a series of salts of a particular medicinal compound, for use in making a composition of matter comprising said salt and a cyclodextrin, said method comprising:

a. obtaining said series of salts;

b. determining the equilibrium solubility, in aqueous cyclodextrin solution, of each of said salts in said series; and

c. selecting, as said useful salt, a salt in said series having a solubility in said cyclodextrin solution equal to or greater than a desired target solubility.

3. A method of determining a useful salt, from within a series of salts of a particular medicinal compound, for use in making a composition of matter comprising an inclusion complex of said salt in a cyclodextrin, said method comprising:

a. determining a quantity of said medicinal compound required for therapeutic efficacy;

b. choosing a maximum total dose in which to administer said quantity of medicinal compound;

c. calculating the minimum required solubility of a salt of said compound necessary to formulate said maximum total dose;

d. obtaining said series of salts;

e. determining the equilibrium solubility of each of said salts in said cyclodextrin; and

f. selecting, as said useful salt, a salt from said series having an equilibrium solubility in said cyclodextrin sufficient to permit making a total dose equal to or less than said maximum total dose.